Acute Lymphoblastic Leukemia in Adults

71

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71.1 Definition and Epidemiology

ALL is a malignant transformation and proliferation of lymphoid progenitor cells in the bone marrow, blood, and extramedullary sites. While 80% of ALL occurs in children, it represents a devastating disease in adults. The incidence of ALL is bimodal, with the first peak occurring in childhood and a second peak occurring around 50 years. The estimated overall incidence of ALL and lymphoblastic lymphoma in Europe is 1.28 per 100,000 individuals annually, with significant age-related variations (0.53 at 45–54 years, ~1.0 at 55–74 years, and 1.45 at 75–99 years) (Terwilliger and Abdul-Hay 2017).

71.2 Diagnosis

Typical but nonspecific clinical manifestations of patients with ALL are constitutional symptoms, bleeding, infections, and/or bone pain, with less than 10% of individuals having symptomatic CNS involvement at diagnosis (Lazarus et al. 2006). Mature B-cell ALL can also present as an extramedullary (e.g., GI or testicular involvement) disease. Mediastinal mass with wheezing and stridor can be a presenting feature of T-lineage ALL. For diagnostic purposes, the addition of flow cytometry to the morphologic identification of neoplastic lymphoblasts is essential for classification of ALL.

71.3 Classification

In 1997, the WHO proposed a composite classification in attempt to account for morphology and cytogenetic profile of the leukemic blasts and identified three types of ALL: B-lymphoblastic, T-lymphoblastic, and Burkitt cell leukemias. Later revised in 2008, Burkitt cell leukemia was eliminated as it is no longer seen as a separate entity from Burkitt lymphoma, and B-lymphoblastic leukemia was divided into two subtypes: B-ALL with recurrent genetic abnormalities and B-ALL not otherwise specified. B-ALL with recurrent genetic abnormalities is further delineated based on the specific chromosomal rearrangement present. In 2016, two new provisional entities were added to the list of recurrent genetic abnormalities, and hypodiploid was redefined as either low hypodiploid (<40 chromosomes) or hypodiploid with *TP53* mutations.

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71.4 Risk Factors

Historically, age and white blood cell count at the time of diagnosis have been used to risk stratify patients. Increasing age portends a worse prognosis. Patients over 55 years have particularly poor outcomes, with only 10–15% long-term survival (Rowe et al. 2015). In most studies the cut point for high-risk ALL has been 30×10^9/L for B-cell precursor ALL and 100×10^9/L for T-cell precursor ALL, respectively.

According to the maturation marker profile measured by *immunophenotyping*, both entities, B- and T-cell precursor ALL, can be classified as less mature ALL, which are associated with an inferior prognosis compared to the more mature subtypes. In B-lineage ALL, the most important markers for subclassification are CD19, CD20, CD22, CD24, and CD79a. The earliest B-lineage markers are CD19, CD22 (membrane and cytoplasm), and CD79a. A positive reaction for any two of these three markers, without further differentiation markers, identifies pro-B ALL. The early T-cell precursor ALL is a subtype of high-risk ALL defined by reduced expression of T-cell markers (CD1a, CD8, and CD5) and aberrant expression of myeloid or stem cell markers (Chiaretti et al. 2014).

Cytogenetics represents an important part of ALL classification (Moorman et al. 2007). Probably the most well-known aberration in acute leukemia, associated with a high-risk disease, is Philadelphia chromosome-positive ALL. This aberration is present in approximately 20% to 30% of adults with ALL. It can be detected as the translocation t(9;22)(q34;q11) by conventional karyotyping including FISH and/or by detection of the *BCR-ABL1* rearrangement by PCR. In addition, aberrations like t(4;11)(q21;q23) or *MLL* rearrangements at 11q23 and hypodiploidy/low hypodiploidy (and the strictly related near-triploid group) fall also into the poor-risk cytogenetic category, with an overall disease-free survival rate of about 25%. The prognostic relevance of a complex karyotype (five or more chromosomal aberrations) in ALL remains controversial among different study groups.

Most ALL cases harbor multiple somatic *genetic alterations* in addition to gross chromosomal alterations. Chromosomal rearrangements and aneuploidy are early events in leukemogenesis, with DNA copy number alterations and sequence mutations acquired subsequently. Genes encoding transcriptional regulators of lymphoid development are among the most frequently mutated genes, particularly in B-linage ALL. Several key genetic alterations may be associated with an inferior outcome, e.g., the IKZF1 alterations with treatment failure (Dhedin et al. 2015). However, these findings have to be verified in further prospective trials.

Persistence of *MRD* after induction/early consolidation, between weeks 4 and 22 and with a level $\geq 10^{-4}$, indicates intrinsic drug resistance (Holowiecki et al. 2008). MRD is evaluable using either multichannel flow cytometry or the real-time quantitative polymerase chain reaction (RQ-PCR). Aberrant phenotypes are identified on the basis of different combinations and/or asynchronous expression and/or variable intensity staining of several antigens. PCR targets are fusion genes associated with chromosomal abnormalities (e.g., BCR-ABL, MLL-AF4) or rearranged immunoglobulin or T-cell receptor sequences (TCR β, γ, δ, IgH, IgK-Kde) unique to each patient with ALL. A MRD level exceeding 10^{-4} after 2–3 months of treatment is an indicator for a high-risk disease, whereas an increase above 10^{-3} represents a very high risk for relapse (Bruggemann et al. 2010).

71.5 Prognostic Factors Used to Indicate Allo-HSCT in CR1

Although data from prospective randomized studies are lacking and are most likely impossible to obtain due to the small numbers in some subgroups, some patient–/disease-related risk factors might be an indication for an allo-HSCT in the first remission.

Prognostic factor	Indication of allo-HSCT if
Age	>40 years
High WBC count at diagnosis	$>30 \times 10^9$/L in BCP-ALL $>100 \times 10^9$/L in T-ALL
Poor-risk cytogenetics	Ph chromosome t(4;11)(q21;q23) t(8;14)(q24.1;q32) Complex karyotype Low hypodiploidy/near triploidy

Prognostic factor	Indication of allo-HSCT if
ALL subtypes with poor prognosis	Early T-cell precursor ALL (Ph-like ALL) (limited data, pending trials)
High-risk genetics	IKZF1 deletion in B precursor ALL (NOTCH1/FBXW7; N/K-RAS; PTEN genetics in T-ALL (Trinquand et al. 2013)) (limited data, pending trials)
Failure to attain CR	Within 4 weeks of therapy
Minimal residual disease	$>1 \times 10^{-4}$ after two courses of therapy Reappearance of MRD marker (no MRD marker at initial diagnosis)

71.6 First-Line Treatment

The first-line chemotherapy usually consists of induction, treatment intensification/consolidation, and long-term maintenance, with CNS prophylaxis given at intervals throughout therapy. The goal of induction therapy is to achieve CR remission and to restore normal hematopoiesis. The backbone of induction therapy typically includes VCR, PRD, and an anthracycline with or without L-asp and CY.

Intensive postremission consolidation therapies improve outcome. Most study groups recommend six to eight courses, two to four of which contain high-dose MTX, Ara-C, and L-asp, and one to two represent reinduction blocks.

Postremission consolidation is most often followed by long-term maintenance with daily oral mercaptopurine and weekly MTX for 2 years or longer, sometimes with periodic applications of, e.g., VCR, PRD, or other drugs (Bassan and Hoelzer 2011).

The addition of RTX to the induction and consolidation therapy for patients with B-precursor ALL (Maury et al. 2016), as well as imatinib for patients with Ph-positive ALL (Fielding et al. 2014), has significantly improved the outcome in these subgroups.

These modern regimens usually allow remission rates of 90% and more in patients with standard-risk ALL. However, in patients of older age (e.g., >45 years) treated with pediatric-inspired protocols, significantly higher rate of chemotherapy-related events compared to younger patients occurs, and response rates decrease.

The introduction of novel agents like nelarabine for patients with T-precursor ALL and blinatumomab and inotuzumab ozogamicin for B-precursor ALL, as part of the frontline therapy, is currently being evaluated in prospective trials.

71.7 Second-Line Treatment

While 85–90% of patients go into remission after induction therapy, there are subsets that are refractory to induction therapy. In addition, many of the patients with complete remission will have a relapse, and only approximately 30–50% will have disease-free survival lasting 3 years or longer. Conventional standard chemotherapy regimens for adults with relapsed or refractory B-cell ALL are associated with rates of CR of 31–44% when they are the first salvage therapy administered after an early relapse and 18–25% when they are the second salvage therapy (Gokbuget et al. 2016). Because CR is typically a prerequisite for subsequent allo-HSCT, the low rates of CR associated with conventional chemotherapy regimens mean that few adults with relapsed or refractory (R/R) B-cell ALL (5–30%) proceed to HSCT, which is considered to be the main goal after salvage treatment because it is the only potentially curative treatment option.

Recently, two randomized trials comparing conventional salvage regimens with novel immunotherapy-based therapies, the Tower trial (Kantarjian et al. 2017) with blinatumomab (targeting CD19) and the INO-VATE ALL trial (Kantarjian et al. 2016) with inotuzumab ozogamicin (targeting CD22), demonstrated significantly higher remission rates (up to 80%) for patients with R/R B-precursor ALL treated with either antibody-based therapy. Moreover, these novel treatments showed a favorable toxicity profile compared to conventional chemotherapies and allowed the treatment, of many of the patients, in an outpatient setting. Both trials defined a new standard therapy option in patients with R/R B-precursor ALL. Conventional chemotherapy might be still a reasonable option in patients with late relapse. However, with regard to treatment toxicity and option of outpatient

treatment, antibody-based therapies should be discussed with the patients, if available.

In patients with R/R Ph + ALL, usually treated with imatinib as part of the first-line treatment, molecular testing of mutations leading to the resistance to particular tyrosine kinase inhibitors (TKIs) should be performed. According to these results, a second-generation TKI (e.g., dasatinib or ponatinib) should be chosen as salvage therapy.

Anti-CD19 chimeric antigen receptor (CAR)-expressing T cells have proved extremely effective against R/R B precursor ALL, at least in children and young adult patients with up to 70–90% response rates reported (Maude et al. 2018; Park et al. 2018). With lacking comparative trials, highly selected patients, and a clinically relevant toxicity profile (e.g., severe cytokine release syndrome, neurotoxicity, and long-lasting B-cell depletion), CAR-T cells have to be evaluated in further prospective trials.

Despite advantages in the treatment of B-precursor ALL, treatment options for patients with R/R T-precursor ALL are limited. So far, there is no agreed standard of care in adults with relapsed T-cell ALL. Standard chemotherapy regimens such as FLAG (FLU, Ara-C, and G-CSF) ± idarubicin only result in 30% to 40% response rates with 6 months median OS in responders. Nelarabine as monotherapy or in combination with other chemotherapeutic agents has shown promising response rates and is a reasonable option (Gokbuget et al. 2011(Gokbuget et al. 2011)).

Patients with persisting MRD or reappearance of their MRD marker without evidence of a hematological relapse have usually an indication for an allo-HSCT. However, treatment of MRD prior to transplant to potentially optimize outcome after HSCT should be discussed for patients in case of high/increasing MRD and particularly for those with an option for a targeted therapy (e.g., change of TKI therapy in patients with Ph + ALL of blinatumomab).

71.8 Autologous HSCT

71.8.1 Indication

Auto-HSCT is not considered a standard therapy for adult ALL. Optional for patients with MRD-negative high-risk ALL, not eligible for allo-HSCT.

71.8.2 Conditioning

Fractionated TBI (e.g., 6 × 2 Gy) in combination with CY and/or VP.

71.8.3 Results

In some trials, patients excluded from allo-HSCT were randomly assigned between chemotherapy and auto-HSCT. In one of the largest studies, chemotherapy proved superior, while a marginal superiority of auto-HSCT was ascertained in high-risk patients in another (Goldstone et al. 2008). In a European retrospective analysis on auto-HSCT, a cohort of patients who were MRD negative had a significantly better survival compared to those being MRD positive. Results of another retrospective study comparing auto- and allo-HSCT for adults with Philadelphia-positive ALL in first complete molecular remission showed similar survival rates for both groups (higher rate of relapse after auto-HSCT and higher rates of death in remission after allo-HSCT).

It remains a matter of debate if the MRD-negative patients in these retrospective trials would have shown similar results with conventional chemotherapy. The value of high-dose therapy, particularly in ALL patients being early MRD negative after induction therapy, has to be evaluated in prospective trials.

71.9 Allogeneic HSCT

71.9.1 Indication

Standard therapy for patients with high-risk ALL in CR1 (see Sect. 71.5) and standard therapy for patients with subsequent remission after induction failure or relapsed ALL (Dhawan and Marks 2017). Optional for patients with standard-risk ALL in CR1 and unexpectable treatment-related toxicities (e.g., prolonged severe cytopenia), which preclude continuation of conventional therapy. Optional for patients with refractory/active ALL (Pavlu et al. 2017).

71.9.2 Conditioning

For fit patients <45 years and no relevant comorbidities, preferable fractionated TBI (cumulative dose of 12–13 Gy) in combination with CY or

VP (Marks et al. 2006); alternative BU (preferable IV BU targeted plasma-drug level monitoring) in combination with CY. For patients aged 45 years and older, dose-adapted/dose-reduced conditioning should be considered. So far, no standard regimen has been established. Reasonable options are TBI-based therapies (e.g., 8 Gy TBI in combination with FLU or CY) and MEL-, BU-, or TREO-based conditioning regimes.

Especially patients transplanted beyond first remission are at risk for severe transplant-related toxicities with cumulative incidence of death in remission exceeding 30% and more. Consequently, dose-reduced conditioning regimes should be discussed in patients being in a MRD-negative subsequent remission after treatment with novel antibody-based salvage therapies. Moreover, conditioning therapies associated with significant toxicities (e.g., SOS/VOD for patients treated with inotuzumab ozogamic) must be avoided (Kebriaei et al. 2018).

71.9.3 Donor

MSD, HLA-MUD (at least matched for HLA-A, HLA-B, HLA-C, and DR), HLA-MMUD, haploidentical donor. In patients with HLA-MMUD, a transplant with UCB (Marks et al. 2014) or from haploidentical donor (Santoro et al. 2017) may be the better choice, particularly in those cases with >1 HLA-antigen-mismatched donor (Figs. 71.1 and 71.2).

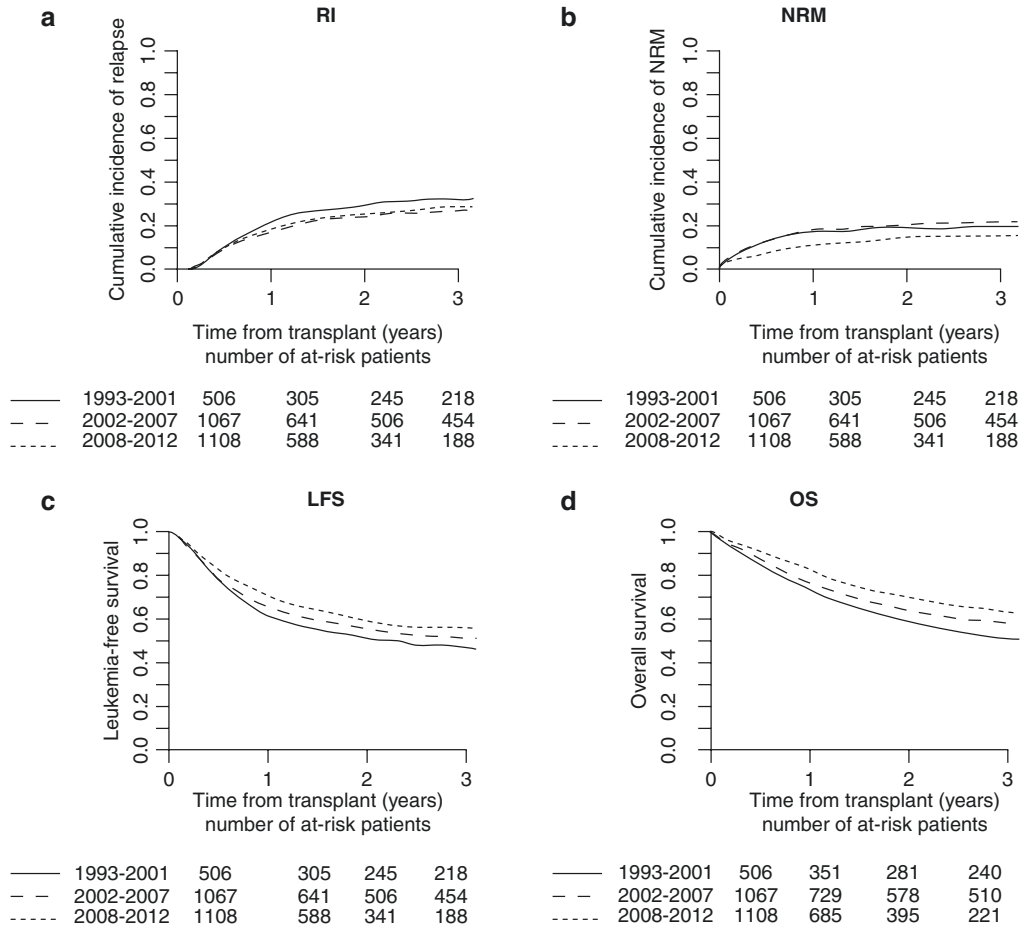

Fig. 71.1 Outcome of *matched sibling donor*—HSCT adults with ALL in CR1. Changes over time in the period 1993–2012. (**a**) Relapse incidence (RI), (**b**) non-relapse mortality (NRM), (**c**) leukemia-free survival (LFS), (**d**) overall survival (OS) (Giebel et al. 2017)

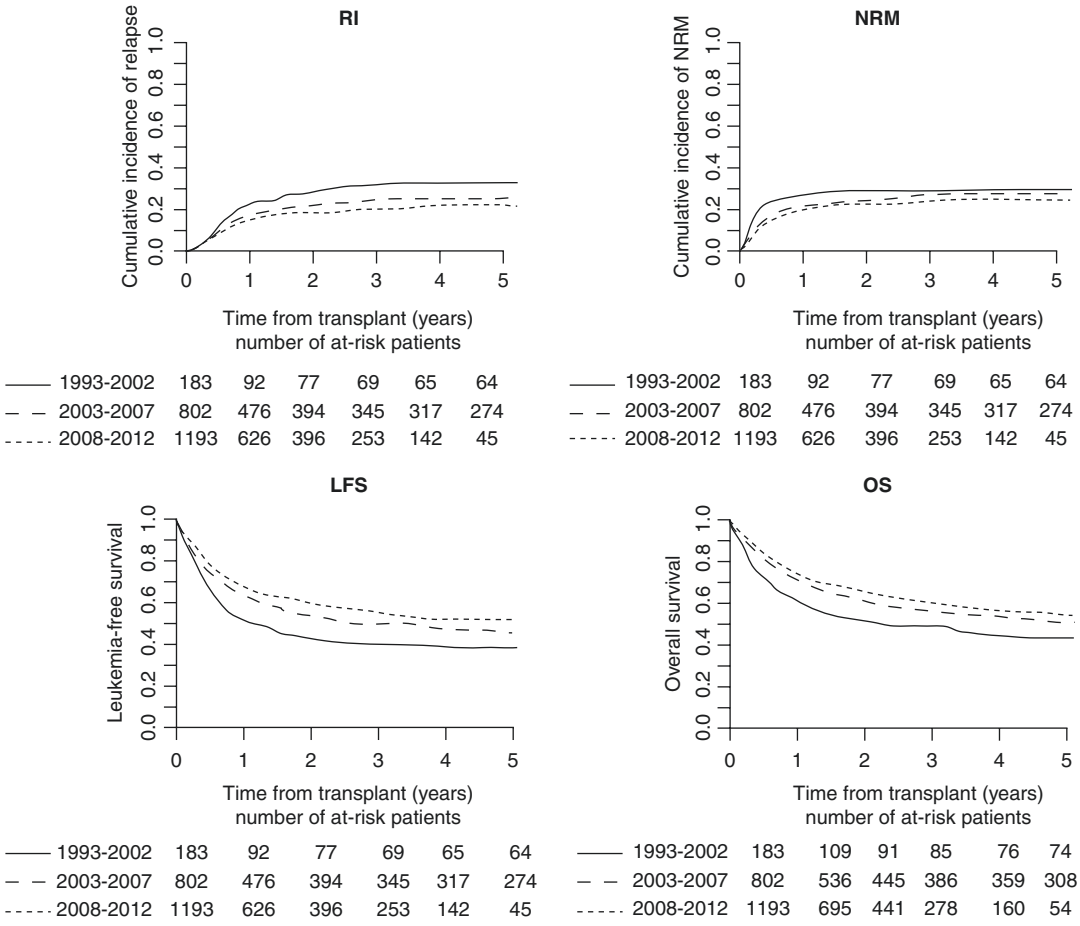

Fig. 71.2 Outcome of *matched sibling donor*—hematopoietic cell transplantation for adults with acute lymphoblastic leukemia (ALL) in first complete remission (CR1). Changes over time in the period 1993–2012. (**a**) Relapse incidence (RI), (**b**) non-relapse mortality (NRM), (**c**) leukemia-free survival (LFS), (**d**) overall survival (OS) (Giebel et al. 2017)

71.9.4 Stem Cell Source

Most likely no relevant difference with regard to GvHD between BM and PBSC as transplant source from an unrelated donor when ATG is part of the conditioning. Faster engraftment and low risk of graft failure with PBSC.

71.9.5 GvHD Prophylaxis

CSA + MTX or CSA + MMF are standard options. ATG should be considered in all patients receiving an allograft from an URD and can be discussed in patients transplanted from an MSD. For haplo-HSCT, using T cell replete allografts combined with post transplant cyclophosphamide (to eliminate alloreactive T cells while sparing other T cells, leading to faster immune reconstitution) is an established option.

71.9.6 Maintenance

For patients with Ph + ALL, maintenance with TKI after allo-HSCT should be applied as a prophylactic or preemptive therapy. At least in patients with B-precursor ALL and positive findings for MRD after allo-HSCT, preemptive therapies with antibodies/antibody-drug conjugates or CAR-T cells are valuable options to be evaluated in prospective trials.

Key Points

Allo-HSCT indicated in	– CR1: high-risk ALL[a] – >CR1: all patients with no contraindication for allogeneic HSCT	
Donor	MSD > MUD > MMUD > Haplo	
Conditioning	– <45 years: TBI/CY; TBI/VP; IV BU/CY. TBI probable associated with lower relapse rates, TBI dose for patients <45 years: cumulative 12–13 Gy – >44 years (or <45 + contraindication for MAC) FLU/IV BU; FLU/MEL; FLU/TBI 8 Gy; FLU/TREO[b]	
Source of SC	PB/BM	
GvHD Proph.	CSA + MTX or CSA + MMF (ATG in MUD or MMUD, consider ATG in MRS)	
Maintenance	Consider TKI in case of Ph + ALL	
TRM	CR1 (age 18–55 year)	MSD: 11–24% (2 year) MUD: 18–29% (2 year)
	CR1 (age >60 year)	MSD: approx. 23% (3 year) MUD: approx. 24% (3 year)
REL	CR1 (age 18–55 year)	MSD: 23–32% (2 year) MUD: 14–21% (2 year)
	CR1 (age >60 year)	MSD: approx. 47% (3 year) MUD: approx. 35% (3 year)
OS	CR1 (age 18–55 year)	MSD: 60–76% (2 year) MUD: 62–70% (2 year)
	CR1 (age >60 year)	MSD: approx. 39% (3 year) MUD: approx. 46% (3 year)
	>CR1[c]	MSD: 8–60% MUD: 10–50%

[a]Definition of "high risk" differs between study groups; most important risk factors: persisting MRD after two courses of therapy, high-risk cytogenetic, early T-cell precursor ALL
[b]For patients treated with inotuzumab ozogamicin, avoid regimens associated with SOS/VODS
[c]Data beyond CR1 are very limited

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